Review Article

Drug Therapy

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CALCIUM-ANTAGONIST DRUGS

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D RUGS classified as calcium antagonists or calcium-channel blockers were introduced into clinical medicine in the 1960s and are now among the most frequently prescribed drugs for the treatment of cardiovascular diseases.[1] Although the currently available calcium antagonists are chemically diverse, they share the common property of blocking the transmembrane flow of calcium ions through voltage-gated L-type (slowly inactivating) channels.[2] These drugs have proved effective in patients with hypertension, angina pectoris, and cardiac arrhythmias and may be beneficial in patients with left ventricular diastolic dysfunction, Raynaud's phenomenon, migraine, preterm labor, esophageal spasm, and bipolar disorders.

L-TYPE CALCIUM CHANNELS

All calcium antagonists bind to the α_{1c} subunit of the L-type calcium channel (Fig. 1), which is the main pore-forming unit of the channel. This subunit is associated with a disulfide-linked $\alpha_2\delta$ subunit and an intracellular β subunit. The $\alpha_2\delta$ and β subunits modulate the α_{1c} subunit. The phenylalkylamine (verapamil-like) calcium antagonists bind to transmembrane segment 6 of motif IV (IVS6), the benzothiazepine (diltiazem-like) calcium antagonists bind to the cytoplasmic bridge between motif III (IIIS) and motif IV (IVS), and the dihydropyridine (nifedipine-like) calcium antagonists bind to transmembrane segment 6 of both motif III (IIIS6) and motif IV (IVS6) (Fig. 1).[3]

The L-type calcium channel was first isolated from cardiac muscle and has since been found in vascular

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smooth muscle (arteriolar and venous), nonvascular smooth muscle (bronchial, gastrointestinal, genitourinary, and uterine), and noncontractile tissues (pancreas, pituitary, adrenal glands, salivary glands, gastric mucosa, white cells, platelets, and lacrimal tissue). Blockade of L-type channels in vascular tissues results in the relaxation of vascular smooth muscle and in cardiac tisssue results in a negative inotropic effect. The ability of these drugs to decrease smooth-muscle and myocardial contractility results in both clinically desirable antihypertensive and antianginal effects and undesirable myocardial depression.

Other calcium channels with electrophysiologic properties have also been identified. These channels, to which the calcium antagonists do not bind, include the N-type channels in neuronal tissue, P-type channels in Purkinje tissues, and T-type (transient potential) channels in cardiac nodal structures and vascular smooth muscle.[4,5]

Regulation of the L-type channels may differ in different types of cells. In cardiac myocytes, these channels are activated by catecholamines and other stimuli that activate adenylyl cyclase or cyclic adenosine monophosphate–dependent protein kinase.[6-8] In contrast, these stimuli activate, inhibit, or have no effect on L-type calcium channels in vascular and visceral smooth-muscle beds, depending on the experimental conditions.[9,10] L-type channels are also activated by the α_1-adrenergic system,[11] angiotensin II,[12] and endothelin.[13] As an in vivo correlate of these findings, calcium antagonists block the responses of vascular smooth muscle to phenylephrine, angiotensin II, and endothelin-1 in humans.[14,15] In addition to hormonal activation by means of signal-transduction pathways, L-type channels may be directly activated at the plasma membrane by guanine nucleotide–binding (G) proteins produced in response to hormone binding to its receptors.

CALCIUM CHANNELS AND CELL GROWTH

L-type (and T-type) calcium channels seem to have a role in cellular growth and proliferation in addition to their role in the acute changes in ion flux associated with changes in membrane potential. Several calcium antagonists, and possibly all, can inhibit the growth and proliferation of vascular smooth muscle and fibroblasts. All classes of calcium antagonists decrease the growth of vascular smooth-muscle cells in vitro and in animals, as measured by decreased uptake of uridine (RNA synthesis) and incorporation of leucine (protein synthesis) at drug concentrations associated with clinical effects.[16,17] Calcium antagonists may also inhibit the synthesis of extracellular-
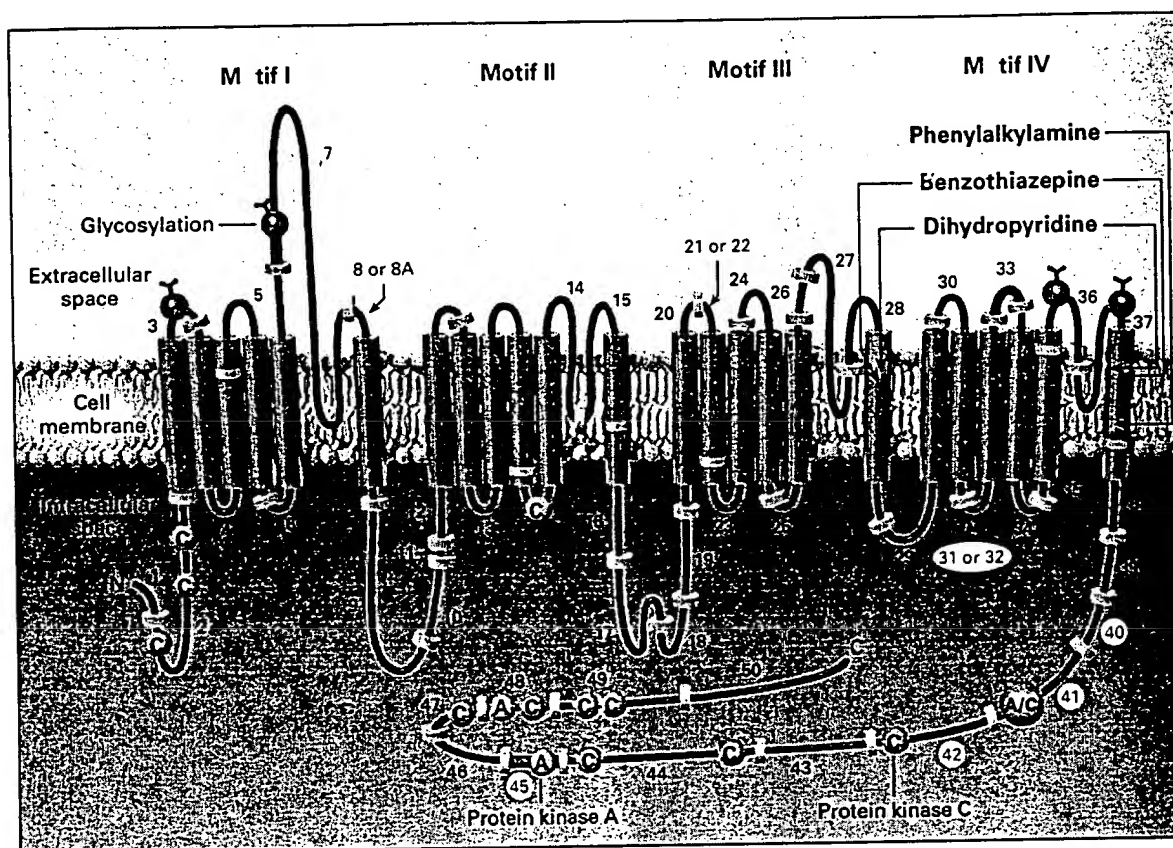
Figure 1. Proposed Arrangement of the Polypeptide Chain of the Channel-Forming α_{1c} Subunit of the L-Type Calcium Channel in Humans.

The four repetitive motifs (I, II, III, and IV) each consist of six putative transmembrane segments. Both the N terminal and the C terminal point to the cytoplasm. Gold rings separate the segments encoded by numbered exons. The transmembrane segments encoded by alternative exons 8 or 8A, 21 or 22, and 31 or 32 are shown. Sequences encoded by invariant exons 7, 33, and 45, which are subject to constitutive splicing, are blue. Exons 40, 41, and 42 are subject to alternative splicing. Putative sites of glycosylation and of phosphorylation involving protein kinase C (C) and protein kinase A (A) are shown, as are the discrete binding areas of the three types of calcium antagonists — phenylalkylamine (verapamil-like), benzothiazepine (diltiazem-like), and dihydropyridine (nifedipine-like).

matrix collagen proteins,[18] and they prevent atherosclerosis in animals with hyperlipidemia.[19] However, in most clinical studies calcium antagonists did not reverse or slow the progression of atherosclerosis.[20,21]

CLINICAL PHARMACOLOGY

Nine calcium antagonists are currently marketed in the United States for the treatment of hypertension, angina, and supraventricular arrhythmias, and one — nimodipine — is approved for short-term use in patients with subarachnoid hemorrhage (Table 1). Only diltiazem, nicardipine, and verapamil are available in intravenous formulations, and long-term treatment with calcium antagonists is usually by the oral route.

Pharmacokinetics

After oral administration, the bioavailability of these drugs varies depending on first-pass metabolism in the intestinal wall and liver.[22] All are metabolized to less active metabolites in the liver by oxidative pathways, predominantly by cytochrome P-450 CYP3A, a subgroup of the cytochrome P-450 enzyme family, and to a lesser extent by other members of this enzyme family.[23-25] All calcium antagonists, with the exception of diltiazem and nifedipine, are administered as racemic mixtures, with one active and one inactive stereoisomer with respect to blockade of L-type calcium channels.[26] The cytochrome P-450 CYP3A enzymes metabolize each isomer at a different rate, resulting in stereoselective drug clearance.[27] Hepatic biotransformation of calcium antagonists such as verapamil may be greater in women than men.[28]

Pharmacodynamics

All currently available calcium antagonists cause vasodilation, with lowering of blood pressure. Their rel-

TABLE 1. CLINICAL DOSING INFORMATION FOR THE CALCIUM ANTAGONISTS APPROVED FOR USE IN THE UNITED STATES.

DRUG	APPROVED INDICATIONS	FORM AND DOSE	TIME TO PEAK EFFECT	ELIMINATION HALF-LIFE
			hours	
Amlodipine	Angina, hypertension	Tablet; 2.5–10 mg once daily	6–12	30–50
Bepridil*	Refractory angina	Tablet; 200–400 mg once daily	2–3	26–64
Diltiazem†	Angina, hypertension	Immediate-release tablet; dose varies depending on indication	0.5–1.5	2–5
	Atrial fibrillation or flutter, paroxysmal supraventricular tachycardia	Sustained-release tablet; 180–480 mg once daily	6–11	2–5
Felodipine	Hypertension	Sustained-release tablet; 2.5–10 mg once daily	2.5–5	11–16
Isradipine	Hypertension	Tablet; 2.5–10 mg twice daily	1.5	8–12
Nicardipine†	Angina, hypertension	Immediate-release tablet; 20–40 mg three times daily	0.5–2.0	8
	Angina, hypertension	Sustained-release tablet; 60–120 mg once daily	?	8
Nifedipine	Angina, hypertension	Immediate-release capsule; dose varies depending on indication	0.5	2
	Angina, hypertension	Sustained-release capsule; 30–120 mg once daily	6	2
Nimodipine	Subarachnoid hemorrhage	Capsule; 60 mg every 4 hr for 21 days	1	1–2
Nisoldipine	Hypertension	Sustained-release tablet; 20–40 mg once daily	6–12	7–12
Verapamil†	Angina, hypertension	Immediate-release tablet; dose varies depending on indication	0.5–1.0	4.5–12
	Atrial fibrillation or flutter, paroxysmal supraventricular tachycardia	Sustained-release tablet; 120–480 mg once daily	4–6	4.5–12

*Bepridil is indicated only for patients with angina that is refractory to treatment with other drugs.

†This drug is also available in an intravenous formulation, with a time to peak effect ranging from 5 to 15 minutes after administration.

ative potency as vasodilators varies, with nifedipine typically considered the most potent of the dihydropyridines, and verapamil, diltiazem, and bepridil having less potency. In vitro, several calcium antagonists (e.g., nifedipine, nisoldipine, and isradipine) bind with some selectivity to the L-type calcium channel in blood vessels, whereas verapamil binds equally well to cardiac and vascular L-type calcium channels.[29,30] The relevance of these in vitro findings to treatment in humans is not known. In vitro, all classes of calcium-channel blockers depress sinus-node activity and slow atrioventricular conduction, yet only verapamil and diltiazem delay atrioventricular conduction or cause sinus-node depression at doses used clinically. Similarly, all classes cause concentration-dependent decreases in myocardial contractility in vitro, but only verapamil and diltiazem do so in vivo. The disparities between the in vitro and in vivo effects are probably explained by the sympathetic activation that occurs in response to the vasodilation induced by dihydropyridines, which blunts their direct negative chronotropic and inotropic effects.

THERAPEUTIC USES AND CONTROVERSIES

Hypertension

In the United States, amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil are currently approved for the treatment of patients with hypertension (Table 1). Each of these drugs lowers diastolic blood pressure during long-term oral administration at the recommended doses. Most are available in long-acting formulations that permit once-daily administration. In the United States, calcium antagonists are currently recommended as first-line therapy for hypertension only if there is a compelling reason not to administer a thiazide diuretic or a beta-blocker.[31] This recommendation is based on the lack of evidence that treatment with calcium antagonists reduces hypertension-related morbidity and mortality. A reported exception is the decrease in stroke with the use of nitrendipine for the treatment of systolic hypertension in the elderly in the Systolic Hypertension in Europe Trial.[32] However, nitrendipine is not available in the United States.

Several retrospective case–control studies have suggested that treatment of hypertension with primarily short-acting calcium antagonists may be associated with an increased incidence of myocardial infarction.[33,34] These data have been unconvincing to many.[35,36]

Concomitant with these reports, the prospective, randomized Multicenter Isradipine Diuretic Atherosclerosis Study, which was designed to compare the rates of progression of carotid atherosclerosis in patients treated with hydrochlorothiazide and those given isradipine, demonstrated, as a secondary finding, that the isradipine-treated patients had an increased incidence of both angina pectoris and a composite group of vascular events.[37] However, the data suggesting an association between calcium-antagonist therapy and myocardial infarction in patients with hypertension cannot be considered conclusive. A potential mechanism for these outcomes, if they are real, may be reflex sympathetic stimulation of β-adrenergic receptors. Sympathetic stimulation occurs after rapid intravenous administration of verapamil, diltiazem, or nifedipine or oral administration of short-acting dihydropyridines in normal subjects and patients with hypertension.[38,39] Less well recognized is the evidence of sympathetic stimulation during the administration of sustained-release nifedipine.[40]

Patients with diabetes mellitus may represent a special subgroup for whom calcium-antagonist therapy increases the risk of cardiovascular complications. Further analysis of the data from the Multicenter Isradipine Diuretic Atherosclerosis Study indicated that the adverse effects of isradipine occurred in patients with high glycosylated hemoglobin values, suggesting that there is a relation between glucose intolerance and an increased risk of vascular events.[41] Another prospective comparison of enalapril and nisoldipine in patients who had hypertension and type 2 diabetes revealed a higher incidence of myocardial infarction among the patients who received nisoldipine.[42] Similarly, in the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial, a prospective comparison of fosinopril and amlodipine in hypertensive patients of all ages who had type 2 diabetes, the overall rate of cardiovascular events was higher among the patients who received amlodipine.[43] The results of these studies weaken arguments that the adverse outcomes associated with calcium antagonists are limited to the rapid-acting and the short-acting drugs,[44] because both sustained-release nisoldipine[42] and isradipine — with an elimination half-life of 8 to 12 hours[37] — have been associated with similar adverse outcomes.

In contrast, retrospective analyses of the relative benefits of antihypertensive-drug therapy in elderly patients who had systolic hypertension with or without diabetes found that twice-daily nitrendipine had greater cardiovascular benefit in patients with diabe-

tes than in those without diabetes.[45] The results of this trial are insufficient to permit conclusions to be drawn regarding the relative benefit of nitrendipine alone as compared with nitrendipine in combination with other types of antihypertensive therapy (angiotensin-converting–enzyme inhibitors or diuretics). Nitrendipine is currently not approved for marketing in the United States. For U.S. practitioners, the available data do not support a recommendation that a calcium antagonist should be the first choice for patients who have hypertension and diabetes.

Angina Pectoris

Calcium antagonists are effective in the treatment of both classic angina pectoris and the less frequent vasospastic, or variant, angina (Prinzmetal's angina).[46-48] In the United States, amlodipine, diltiazem, nicardipine, nifedipine, and verapamil are approved for the treatment of angina (Table 1). In addition, bepridil is indicated only for patients with angina that is refractory to treatment with other drugs. With the exception of the rapid-acting formulations, which may occasionally worsen angina, each of these drugs substantially prolongs the time to the onset of angina during exercise, decreases the frequency of episodes of angina, or decreases the need for short-acting nitroglycerin in patients who require long-term oral administration of nitroglycerin. Although calcium antagonists are effective as monotherapy for angina, combined treatment with a calcium antagonist, a nitrate, and a beta-blocker can have an additive effect.[49] Particularly effective combinations for patients with stable angina include either a dihydropyridine and a beta-blocker or verapamil or diltiazem in combination with a nitrate, followed by the addition of a beta-blocker in patients with unsatisfactory control of angina.[49] Calcium-antagonist therapy alone is not effective in patients with unstable angina.[50]

The comparative effects on morbidity or mortality of long-term therapy with various calcium antagonists in patients with stable angina are not known. A retrospective review of data has led to concern that the risk of death may be slightly higher among patients who receive dihydropyridine calcium antagonists.[51]

Supraventricular Arrhythmias

Verapamil and diltiazem are approved for the treatment of patients with supraventricular arrhythmias — specifically for the short- and long-term treatment of atrial fibrillation, atrial flutter, and atrioventricular nodal reentry in patients without accessory bypass tracts (Table 1).[52] Verapamil and diltiazem slow conduction through the atrioventricular node and increase the atrioventricular nodal refractory period, which, in turn, results in the slowing of the ventricular response rate in atrial fibrillation or flutter or in the conversion of atrioventricular nodal reentry tachyarrhythmias to sinus rhythm by disruption of the tim-

ing of the reentry circuit. As with the other effects of verapamil on the blockade of L-type calcium channels, this is a stereospecific effect, with S-verapamil causing a delay in atrioventricular nodal conduction and R-verapamil having little effect.[26-28]

The ability of verapamil and diltiazem to block the actions of the atrioventricular node is more pronounced at faster than slower heart rates, a property termed "use dependency" or "frequency dependency." Verapamil and diltiazem may also cause sinus-node depression. At clinically tolerated doses, dihydropyridine calcium antagonists do not prolong atrioventricular conduction or refractoriness or cause sinus-node depression and therefore are not indicated for the treatment of supraventricular arrhythmias. The different electrophysiologic effects may be due to differing effects on voltage and use dependency between phenylalkylamine and benzothiazepine drugs, on the one hand, as compared with the dihydropyridine drugs, on the other. Alternatively, the differences may be related to differences among the various classes of drugs in their action on T-type calcium channels, which are more prominent in cardiac nodal structures.

Long-term administration of verapamil or diltiazem slows the ventricular response rate and increases exercise tolerance in patients with chronic atrial fibrillation.[52] However, neither drug prevents atrial fibrillation or flutter or completely suppresses episodes of atrioventricular nodal reentry arrhythmia, whether given alone or in combination with digoxin or a beta-blocker. Ongoing trials are evaluating the relative efficacy of controlling the ventricular rate as compared with maintaining sinus rhythm in patients with chronic atrial fibrillation. The results should further elucidate the role of treatment with verapamil and diltiazem.[53,54]

Subarachnoid Hemorrhage

Nimodipine is approved for the treatment of patients who have had subarachnoid hemorrhage, but its usefulness in clinical practice is uncertain. In animals with regional brain ischemia, nimodipine increased regional blood flow and led to a decrease in blood flow in brain tissue.[55] In patients with subarachnoid hemorrhage, the administration of nimodipine resulted in slightly better recovery of function than did placebo.[56] Neither nimodipine nor other calcium antagonists were beneficial in patients with ischemic stroke.[57]

Myocardial Infarction

In vitro studies and experiments in animals have suggested that treatment with calcium antagonists could limit the size of myocardial infarcts or preserve myocardium after ischemia.[58] Their benefit in patients who have had a myocardial infarction is limited. In a large, randomized study of patients who had a nontransmural myocardial infarction, mortality was similar in the diltiazem and placebo groups.[59] In post hoc analyses, the mortality rate was slightly higher among patients with decreased left ventricular function who received diltiazem and slightly lower among patients with normal left ventricular function who received it. More recently, a trend toward a higher rate of cardiac events was reported among patients who were treated with short-acting nifedipine or diltiazem after a myocardial infarction.[60] In contrast, in a large, randomized, placebo-controlled trial of verapamil in patients with myocardial infarction, long-term mortality was lower in the verapamil group,[61] and a retrospective analysis of the results suggested that the benefit was greatest in patients without congestive heart failure.[62] A smaller randomized, placebo-controlled study found that verapamil had no effect on the risk of death but significantly lowered the rates of reinfarction.[63] Trials of longer-acting calcium antagonists found either no adverse effects[64] or beneficial effects.[65]

These studies predated the current therapeutic guidelines for patients with a recent myocardial infarction, which call for the administration of a beta-blocker and aspirin, with or without an angiotensin-converting–enzyme inhibitor.[66] It is therefore difficult to place in perspective the data comparing calcium antagonists with placebo in patients with myocardial infarction. There is agreement that short-acting calcium antagonists are contraindicated, and the available data do not support the routine use of a longer-acting calcium antagonist. However, treatment with verapamil may be appropriate for patients who have contraindications to treatment with beta-blockers.[66]

Risk of Cancer

A retrospective study of older patients with a new diagnosis of cancer suggested that patients who were taking a calcium antagonist had a higher risk of cancer than those who were taking a beta-blocker or an angiotensin-converting–enzyme inhibitor.[67] A series of population-based studies followed; data from the Cardiovascular Health Study suggested that the risk of breast cancer was increased in women who were taking a calcium antagonist.[68] In contrast, studies from Denmark[69] and Scotland[70] and another retrospective study from the United States[71] concluded that calcium-antagonist therapy did not increase the risk of any type of cancer among patients with hypertension.

DRUG INTERACTIONS

Pharmacokinetic Basis

The CYP3A group of cytochrome P-450 isoenzymes has a major role in the oxidative biotransformation of all the calcium antagonists.[23-25] In addition, verapamil inhibits P-glycoprotein–mediated drug transport, which may alter the intestinal absorption of several drugs and their distribution into peripheral tissues and the central nervous system.[72,73]

Reported and possible drug, dietary, and other

TABLE 2. REPORTED OR POSSIBLE INHIBITORY EFFECTS OF CALCIUM ANTAGONISTS ON OTHER DRUGS.*

CALCIUM ANTAGONIST AND DRUG AFFECTED	MECHANISM	PHARMACOKINETIC EFFECT	POTENTIAL CLINICAL EFFECT
Bepridil			
Digoxin	Decreased clearance	Increased serum digoxin concentration	Digoxin toxicity
Verapamil			
Digoxin	Decreased clearance	Increased serum digoxin concentration	Digoxin toxicity
Diltiazem, verapamil			
Carbamazepine	Decreased clearance	Increased serum carbamazepine concentration	Neurotoxicity (dizziness, headache, ataxia, dysarthria)
Antihistamines			
Astemizole	Decreased cytochrome P-450 CYP3A activity	Increased exposure to active drug	Prolongation of corrected QT interval
Terfenadine	Increased bioavailability, decreased clearance	Increased exposure to active drug	Torsade de pointes
Cisapride	Decreased clearance	Increased exposure to active drug	Torsade de pointes
Quinidine	Decreased clearance	Increased exposure to active drug	Torsade de pointes
HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	Decreased clearance	Increased exposure to active drug	Myopathy, rhabdomyolysis
Immunosuppressive drugs Cyclosporine Tacrolimus	Decreased clearance	Increased exposure to active drug	Nephrotoxicity
Beta-blockers Metoprolol Propranolol	Decreased clearance	Increased exposure to active drug	Bradycardia, negative inotropy, cardiac-conduction disturbance, asystole
HIV-protease inhibitors Indinavir Nelfinavir Ritonavir Saquinavir	Decreased clearance	Increased exposure to active drug	Unknown
Theophylline	Decreased metabolic clearance	Increased serum theophylline concentration	Theophylline toxicity

*HMG-CoA denotes hydroxymethylglutaryl–coenzyme A, and HIV human immunodeficiency virus.

types of interactions with calcium antagonists and the underlying mechanism (if known) are shown in Tables 2 and 3. In general, verapamil and diltiazem inhibit the clearance of other substrates of cytochrome P-450 CYP3A (e.g., carbamazepine, cyclosporine, lovastatin, simvastatin, midazolam, triazolam, terfenadine, and astemizole), whereas the dihydropyridine drugs do not. Verapamil and diltiazem can also increase the absorption of drugs such as cyclosporine that are substrates for P-glycoprotein–mediated drug transport.[73,74] This interaction has been exploited clinically by using verapamil or diltiazem to treat hypertension in cyclosporine-treated patients, thus allowing a reduction in the dose of cyclosporine. In vitro data suggest that dihydropyridines are not transported by and do not inhibit P-glycoprotein. Inducers and inhibitors of cytochrome P-450 CYP3A–mediated biotransformation of drugs, however, can affect the metabolism of dihydropyridines as well as verapamil and diltiazem. For example, during treatment with dihydropyridines, the ingestion of large amounts of grapefruit juice may increase the bioavailability of these drugs,[75] but the clinical importance of this interaction is uncertain.[76]

Interactions with Cardiac Glycosides

Verapamil consistently increases serum digoxin concentrations by decreasing the clearance and volume of distribution of the drug, but diltiazem and dihydropyridines do not have this effect.[77,78] The mechanism of this interaction is probably due in part to verapamil-induced inhibition of P-glycoprotein–mediated transport of digoxin into peripheral tissues.[73] Verapamil also decreases the clearance of digitoxin.[78] After verapamil

TABLE 3. REPORTED OR POSSIBLE EFFECTS OF OTHER DRUGS, NUTRIENTS, DISEASE, AND OTHER FACTORS ON CALCIUM ANTAGONISTS.

VARIABLE	CALCIUM ANTAGONIST AFFECTED	MECHANISM	PHARMACOKINETIC EFFECT	POTENTIAL CLINICAL EFFECT
Cimetidine	Verapamil	Decreased clearance	Slight increase in exposure to active drug	Prolongation of PR interval
	Dihydropyridines	Decreased clearance	Slight increase in exposure to active drug	Unknown
Sulfinpyrazone	Verapamil	Decreased clearance	Increased exposure to active drug	Prolongation of PR interval
Rifampin	All types	Increased clearance	Large decrease in exposure to active drug	Decreased calcium-antagonist effect
Phenytoin or phenobarbital	All types	Increased clearance	Decreased exposure to active drug	Possible decrease in calcium-antagonist effect
Ketoconazole or itraconazole	All types	Decreased clearance	Increased exposure to active drug	Possible increase in calcium-antagonist effect
Grapefruit juice	Felodipine, nisoldipine, perhaps other dihydropyridines	Increased bioavailability	Increased exposure to active drug	Possible increase in calcium-antagonist effect
Liver disease	All types	Increased bioavailability, decreased clearance	Increased exposure to active drug	Increased calcium-antagonist effect
Advanced age	All types	Decreased clearance	Increased exposure to active drug	Increased hypotensive effect

therapy is initiated in a patient who is receiving digoxin or digitoxin, the cardiac glycoside should be measured in serum after it has reached a new steady state to determine whether the dose should be reduced.

Pharmacodynamic Interactions

The relatively wide therapeutic index of calcium antagonists makes the clinical importance of all but a few pharmacodynamic interactions quite limited. The following are selected examples of clinically important interactions.

Cardiac Interactions

Treatment with verapamil or diltiazem in combination with amiodarone, digoxin, or a beta-blocker inhibits atrioventricular conduction and sinus-node function more than does treatment with verapamil or diltiazem alone. When the combination of a calcium antagonist and digoxin causes advanced heart block, accelerated atrioventricular junctional escape may occur. Although combined oral treatment with a calcium antagonist and a beta-blocker is usually well tolerated, combined intravenous administration of verapamil and a beta-blocker has resulted in asystole and should not be attempted. In patients with impaired left ventricular function, treatment with verapamil or diltiazem in combination with a beta-blocker can lead to additive negative inotropic effects.[79]

Vascular Interactions

Concomitant administration of a calcium antagonist with other antihypertensive drugs causes an increased antihypertensive effect. In many instances this result may be desired; however, when a calcium antagonist is given in combination with a beta-blocker, sinus-node depression may occur, and when it is given with a diuretic, hypovolemia and postural hypotension may occur.[80]

Noncardiovascular Interactions

Concurrent treatment with lithium and verapamil can predispose patients to lithium neurotoxicity.[81] Nonvascular peripheral edema has been reported during treatment with all calcium antagonists. Gingival hyperplasia may occur in patients who are given a dihydropyridine, but it is rare in those given verapamil or diltiazem. Constipation occurs as a result of relaxation of gastrointestinal smooth muscle and may be more common with verapamil. Headache, which is common in patients who are treated with rapid-acting calcium antagonists, is less common with slow-acting and sustained-release preparations.

SPECIAL CONSIDERATIONS

Older Patients

Calcium antagonists are effective for the treatment of hypertension in older patients.[82] Intravenous administration of verapamil, diltiazem, or amlodipine results in a greater hypotensive effect in older than in younger patients with hypertension at a given drug concentration.[83-85] The clearance of most calcium antagonists is decreased in older patients, as compared with younger patients; this difference results in higher

serum drug concentrations in older patients.[86] This difference may be a factor in the perception that older patients have greater antihypertensive responses to calcium antagonists.[87]

The sinoatrial suppressive effects of verapamil and diltiazem, and the resulting decrease in the heart rate, are also greater in older than in younger patients.[83,84] In contrast, the delay in atrioventricular conduction associated with treatment with verapamil and diltiazem is similar or possibly smaller in older than in younger patients.[83,84] Calcium antagonists are effective for the treatment of angina in older patients; however, few studies have compared responses in older and younger patients.[87]

With respect to morbidity, nitrendipine, a dihydropyridine that is not available in the United States, was associated with a decrease in the risk of stroke among elderly patients in the Systolic Hypertension in Europe Trial.[32] Nonetheless, the benefit of a thiazide diuretic alone or in combination with a beta-blocker or a potassium-sparing diuretic as a treatment for systolic hypertension is similar to that of a calcium antagonist. It is therefore difficult to recommend a dihydropyridine as first-line therapy for isolated systolic hypertension in elderly patients. The observed association between calcium-antagonist therapy and an increased incidence of myocardial infarction may be of particular concern in older patients.

Patients with Diabetes Mellitus

Calcium antagonists are an option for the treatment of hypertension associated with diabetes mellitus because they do not adversely affect glucose metabolism, lipid metabolism, or renal function.[88] Thiazide diuretics and beta-blockers decreased morbidity and mortality among hypertensive patients in multiple studies, each of which included a substantial number of patients with diabetes. In contrast, with the exception of nitrendipine in one study,[45] calcium antagonists simply lowered blood pressure.

Studies of the effect of calcium antagonists on proteinuria and progression of nephropathy in patients with diabetes were prompted by the finding that angiotensin-converting–enzyme inhibitors may slow the progression of diabetic nephropathy[89] and by the demonstration that, in animals, nondihydropyridine calcium antagonists increase renal blood flow and increase glomerular filtration by blocking preglomerular vasoconstriction.[90,91] In relatively small placebo-controlled studies of patients who had hypertension and diabetes, dihydropyridine calcium antagonists did not slow the development of proteinuria or renal failure, but verapamil and diltiazem did.[92,93] In a small study, nifedipine delayed the increase in proteinuria in normotensive patients with diabetes; however, it did so less effectively than lisinopril.[94]

At present, in view of the greater evidence of a benefit of angiotensin-converting–enzyme inhibi-

tors and beta-blockers in patients who have hypertension and diabetes,[95] the relative paucity of data on calcium antagonists in these patients, and the recent finding that the risk of a vascular event may be increased during calcium-antagonist treatment in such patients,[41,42] calcium antagonists cannot be considered as first-line therapy for these patients.

Patients with Congestive Heart Failure

All classes of calcium antagonists have dose-dependent negative inotropic effects in vitro and in animals.[96] In vivo, this action is variably counterbalanced by baroreceptor-mediated reflex responses[97] and the reduction in afterload resulting from the decrease in blood pressure. In vivo, nifedipine has fewer negative chronotropic or inotropic effects than verapamil or diltiazem; however, in long-term studies hemodynamic deterioration occurred in some patients with congestive heart failure who were treated with dihydropyridines,[98,99] and these drugs do not have the benefits associated with treatment with an angiotensin-converting–enzyme inhibitor.[100,101] Because of the potential detrimental effects of calcium antagonists in patients with congestive heart failure and ischemic heart disease, and because only weak data suggest a benefit in patients with nonischemic cardiomyopathy when the calcium antagonist is given in combination with an angiotensin-converting–enzyme inhibitor, calcium antagonists should not be given to patients with congestive heart failure.

Overdose of Calcium Antagonists

Reports of overdoses of all three types of calcium antagonists (verapamil-like, diltiazem-like, and nifedipine-like) have been published, with the greatest number of cases occurring with verapamil.[102] The most common presentation is hypotension and bradycardia, often with second- or third-degree heart block. There are no available agonists; therefore, treatment consists of the removal of the drug from the gastrointestinal tract by gastric lavage and ingestion of activated charcoal and correction of the hypotension and cardiac-conduction abnormalities by the intravenous administration of calcium gluconate or calcium chloride and fluids during electrocardiographic and blood-pressure monitoring. Inotropic and chronotropic drugs may be given as needed. Norepinephrine or amrinone is usually given for inotropic support. Abnormalities in cardiac rhythm and conduction may be more resistant to therapy, and responses to calcium, atropine, or isoproterenol may be insufficient, necessitating temporary transvenous pacing.

CONCLUSIONS

L-type calcium-channel antagonists inhibit the transmembrane flow of calcium, resulting in antagonism of vascular smooth muscle, contraction of myocardial smooth muscle, reduction of blood pres-

sure, and coronary-artery dilation. Calcium antagonists have assumed a major role in the treatment of patients with hypertension or coronary artery disease. Verapamil and diltiazem slow the heart rate and prolong atrioventricular conduction, which can prevent supraventricular arrhythmias in patients without accessory bypass pathways or control the rates of ventricular response in patients with atrial arrhythmias. Because these drugs are metabolized largely by the cytochrome P-450 family of enzymes, drug interactions can occur. The calcium antagonists are highly effective antihypertensive and antianginal drugs and have a role in multidrug therapy for these disorders.

REFERENCES

1. Freher M, Challapalli S, Pinto JV, Schwartz J, Bonow RO, Gheorgiade M. Current status of calcium channel blockers in patients with cardiovascular disease. Curr Probl Cardiol 1999;24:236-40.
2. McDonald TF, Pelzer S, Trautwein W, Pelzer DJ. Regulation and modulation of calcium channels in cardiac, skeletal, and smooth muscle cells. Physiol Rev 1994;74:365-507.
3. Hockermon GH, Peterson BZ, Johnson BD, Catterall WA. Molecular determinants of drug binding and action on L-type calcium channels. Annu Rev Pharmacol Toxicol 1997;37:361-96.
4. Spedding M, Paoletti R. Classification of calcium channels and the sites of action of drugs modifying channel function. Pharmacol Rev 1992;44: 363-76.
5. Striessnig J, Grabner M, Mitterdorfer J, Hering S, Sinnegger MJ, Glossmann H. Structural basis of drug binding to L Ca²⁺ channels. Trends Pharmacol Sci 1998;19:108-15.
6. Reuter H, Scholz H. The regulation of the calcium conductance of cardiac muscle by adrenaline. J Physiol (Lond) 1977;264:49-62.
7. Kameyama M, Hofmann F, Trautwein W. On the mechanism of β-adrenergic regulation of the Ca channel in the guinea-pig heart. Pflugers Arch 1985;405:285-93.
8. Tsien RW, Giles W, Greengard P. Cyclic AMP mediates the effects of adrenaline on cardiac Purkinje fibers. Nat New Biol 1972;240:181-3.
9. Droogmans G, Declerck I, Casteels R. Effect of adrenergic agonists on Ca²⁺-channel currents in single vascular smooth muscle cells. Pflugers Arch 1987;409:7-12.
10. Mitra R, Morad M. Ca²⁺ and Ca²⁺-activated K⁺ currents in mammalian gastric smooth muscle cells. Science 1985;229:269-72.
11. Nelson MT, Standen NB, Brayden JE, Worley JF III. Noradrenaline contracts arteries by activating voltage-dependent calcium channels. Nature 1988;336:382-5.
12. Ohya Y, Sperelakis N. Involvement of a GTP-binding protein in stimulating action of angiotensin II on calcium channels in vascular smooth muscle cells. Circ Res 1991;68:763-71.
13. Goto K, Kasuya Y, Matsuki N, et al. Endothelin activates the dihydropyridine-sensitive, voltage-dependent Ca²⁺ channel in vascular smooth muscle. Proc Natl Acad Sci U S A 1989;86:3915-8.
14. Andrawis NS, Craft N, Abernethy DR. Calcium antagonists block angiotensin II-mediated vasoconstriction in humans: comparison with their effect on phenylephrine-induced vasoconstriction. J Pharmacol Exp Ther 1992;261:879-84.
15. Andrawis NS, Gilligan J, Abernethy DR. Endothelin-1-mediated vasoconstriction: specific blockade by verapamil. Clin Pharmacol Ther 1992;52: 583-9.
16. Andrawis NS, Abernethy DR. Verapamil blocks basal and angiotensin II-induced RNA synthesis of rat aortic vascular smooth muscle cells. Biochem Biophys Res Commun 1992;183:767-73.
17. Schmitt R, Clozel JP, Iberg N, Buhler FR. Mibefradil prevents neointima formation after vascular injury in rats: possible role of the blockade of the T-type voltage-operated calcium channel. Arterioscler Thromb Vasc Biol 1995;15:1161-5.
18. Roth M, Eickelberg O, Kohler E, Erne P, Block LH. Ca⁺⁺ blockers modulate metabolism of collagens within the extracellular matrix. Proc Natl Acad Sci USA 1996;93:5478-82.
19. Henry PD, Bentley KI. Suppression of atherogenesis in cholesterol-fed rabbits treated with nifedipine. J Clin Invest 1981;68:1366-9.
20. Lichtlen PR, Hugenholtz PG, Rafflenbuel W, Hecker H, Jost S, Deckers JW. Retardation of angiographic progression of coronary artery disease by nifedipine: results of the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT). Lancet 1990;335:1109-13.
21. Waters D, Lesperance J, Francetich M, et al. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. Circulation 1990;82:1940-53.
22. Kolars JC, Schmiedlin-Ren P, Schuetz JD, Fang C, Watkins PB. Identification of rifampin-inducible P450IIIA4 (CYP3A4) in human small bowel enterocytes. J Clin Invest 1992;90:1871-8.
23. Kroemer HK, Gautier J-C, Beaune P, Henderson C, Wolf CR, Eichelbaum M. Identification of P450 enzymes involved in metabolism of verapamil in humans. Naunyn Schmiedebergs Arch Pharmacol 1993;348: 332-7.
24. Pichard L, Gillett G, Fabre I, et al. Identification of the rabbit and human cytochromes P-450IIIA as the major enzymes involved in the N-demethylation of diltiazem. Drug Metab Dispos 1990;18:711-9.
25. Guengerich FP, Brian WR, Iwasaki M, Sari M-A, Baarnhielm C, Berntsson P. Oxidation of dihydropyridine calcium channel blockers and analogues by human liver cytochrome P-450 IIIA4. J Med Chem 1991;34: 1838-44.
26. Abernethy DR, Schwartz JB. Pharmacokinetics of calcium antagonists under development. Clin Pharmacokinet 1988;15:1-14.
27. Kroemer HR, Echizen H, Heidemann H, Eichelbaum M. Predictability of the in vivo metabolism of verapamil from in vitro data: contribution of individual metabolic pathways and stereoselective aspects. J Pharmacol Exp Ther 1992;260:1052-7.
28. Schwartz JB, Capili H, Daugherty J. Aging of women alters S-verapamil pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 1994; 55:509-17.
29. Morel N, Buryi V, Feron O, Gomez J-P, Christen M-O, Godfraind T. The action of calcium channel blockers on recombinant L-type calcium channel alpha1-subunits. Br J Pharmacol 1998;125:1005-12.
30. Soldatov NM, Bouron A, Reuter H. Different voltage-dependent inhibition by dihydropyridines of human Ca²⁺ channel splice variants. J Biol Chem 1995;270:10540-3.
31. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413-46. [Erratum, Arch Intern Med 1998;158:573.]
32. Staessen JA, Thijs L, Fagard RH, et al. Calcium channel blockade and cardiovascular prognosis in the European trial on isolated systolic hypertension. Hypertension 1998;32:410-6.
33. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995; 274:620-5.
34. Pahor M, Guralnik JM, Corti MC, Foley DJ, Carbonin P, Havlik RJ. Long-term survival and use of antihypertensive medications in older persons. J Am Geriatr Soc 1995;43:1191-7.
35. Epstein M. Calcium antagonists should continue to be used for first-line treatment of hypertension. Arch Intern Med 1995;155:2150-6.
36. Messerli FH. Case-control study, meta-analysis, and bouillabaisse: putting the calcium antagonist scare into context. Ann Intern Med 1995;123: 888-9.
37. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. JAMA 1996;276:785-91.
38. Jariwalla AG, Anderson EG. Production of ischaemic cardiac pain by nifedipine. BMJ 1978;1:1181-2.
39. Grossman E, Messerli FH. Effect of calcium antagonists on plasma norepinephrine levels, heart rate, and blood pressure. Am J Cardiol 1997; 80:1453-8.
40. Schwartz JB, Caputo G, Abbott J. Early experience with dobutamine stress testing and cardiac cine-tomographic imaging in the elderly: antianginal effects of nifedipine-GITS. J Am Geriatr Soc 1993;41:967-74.
41. Byington RP, Craven TE, Furberg CD, Pahor M. Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. Lancet 1997; 350:1075-6.
42. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52.
43. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.

44. Epstein M. The calcium antagonist controversy: the emerging importance of drug formulation as a determinant of risk. Am J Cardiol 1997;79: Suppl 10A:9-19.

45. Tuomilehto J, Rastenyte D, Birkenhäger WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. N Engl J Med 1999;340:677-84.

46. Stone PH. Calcium antagonists for Prinzmetal's variant angina, unstable angina and silent myocardial ischemia: therapeutic tool and probe for identification of pathophysiologic mechanisms. Am J Cardiol 1987;59: 101B-115B.

47. Stone PH, Gibson RS, Glasser SP, et al. Comparison of propanolol, diltiazem, and nifedipine in the treatment of ambulatory ischemia in patients with stable angina: differential effects on ambulatory ischemia, exercise performance, and anginal symptoms. Circulation 1990;82:1962-72.

48. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. N Engl J Med 1980;302: 1269-73.

49. Cohn PF. Concomitant use of nitrates, calcium channel blockers, and beta-blockers for optimal antianginal therapy. Clin Cardiol 1994;17:415-21.

50. Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both: report of the Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group. Br Heart J 1986;56:400-13.

51. Yusuf S. Calcium antagonists in coronary artery disease and hypertension: time for reevaluation? Circulation 1995;92:1079-82.

52. Lundstrom T, Ryden L. Ventricular rate control and exercise performance in chronic atrial fibrillation: effects of diltiazem and verapamil. J Am Coll Cardiol 1990;16:86-90.

53. Hohnloser SH, Kuck KH. Atrial fibrillation: maintaining stability of sinus rhythm or ventricular rate control? The need for prospective data: the PIAF trial. Pacing Clin Electrophysiol 1997;20:1989-92.

54. The Planning and Steering Committees of the AFFIRM Study for the NHLBI AFFIRM Investigators. Atrial fibrillation follow-up investigation of rhythm management — the AFFIRM study design. Am J Cardiol 1997; 79:1198-202.

55. Uematsu D, Greenberg JH, Hickey WF, Reivich M. Nimodipine attenuates both increase in cytosolic free calcium and histologic damage following focal cerebral ischemia and reperfusion in cats. Stroke 1989;20:1531-7.

56. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 1989;298:636-42.

57. Gelmers HJ, Gorter K, de Weerdt CJ, Wiezer HJA. A controlled trial of nimodipine in acute ischemic stroke. N Engl J Med 1988;318:203-7.

58. Kloner RA, Braunwald E. Effects of calcium antagonists on infarcting myocardium. Am J Cardiol 1987;59:84B-94B.

59. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med 1988;319:385-92.

60. Ishikawa K, Nakai S, Takenaka T, et al. Short-acting nifedipine and diltiazem do not reduce the incidence of cardiac events in patients with healed myocardial infarction. Circulation 1997;95:2368-73.

61. The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction: the Danish Verapamil Infarction Trial II — DAVIT II. Am J Cardiol 1990;66:779-85.

62. Jespersen CM. The effect of verapamil on major events in patients with impaired cardiac function recovering from acute myocardial infarction. Eur Heart J 1993;14:540-5.

63. Rengo F, Carbonin P, Pahor M, et al. A controlled trial of verapamil in patients after acute myocardial infarction: results of the Calcium Antagonist Reinfarction Italian Study (CRIS). Am J Cardiol 1996;77:365-9.

64. The DEFIANT-II Research Group. Doppler flow and echocardiography in functional cardiac insufficiency: assessment of nisoldipine therapy: results of the DEFIANT-II study. Eur Heart J 1997;18:31-40.

65. Hansen JF, Hagerup L, Sigurd B, et al. Cardiac event rates after acute myocardial infarction in patients treated with verapamil and trandolapril versus trandolapril alone. Am J Cardiol 1997;79:738-41.

66. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1996;28:1328-428.

67. Pahor M, Guralnik JM, Salive ME, Corti M-C, Carbonin P, Havlik RJ. Do calcium channel blockers increase the risk of cancer? Am J Hypertens 1996;9:695-9.

68. Fitzpatrick AL, Daling JR, Furberg CD, Kronmal RA, Weissfeld JL. Use of calcium channel blockers and breast carcinoma risk in postmenopausal women. Cancer 1997;80:1438-47.

69. Olsen JH, Sørensen HT, Friis S, et al. Cancer risk in users of calcium channel blockers. Hypertension 1997;29:1091-4.

70. Hole DJ, Gillis CR, McCallum IR, et al. Cancer risk of hypertensive patients taking calcium antagonists. J Hypertens 1998;16:119-24.

71. Rosenberg L, Rao S, Palmer JR, et al. Calcium channel blockers and the risk of cancer. JAMA 1998;279:1000-4.

72. Schinkel AH, Wagenaar E, Mol CAAM, von Deemter L. P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. J Clin Invest 1996;97:2517-24.

73. Doppenschmitt S, Langguth P, Regardh CG, Andersson TB, Hilgendorf C, Spahn-Langguth H. Characterization of binding properties to human P-glycoprotein: development of a [3H] verapamil radioligand-binding assay. J Pharmacol Exp Ther 1999;288:348-57.

74. Hunter J, Hirst BH. Intestinal secretion of drugs: the role of P-glycoprotein, and related drug efflux systems in limiting oral drug absorption. Adv Drug Delivery Rev 1997;25:129-57.

75. Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99:2545-53.

76. Abernethy DR. Grapefruits and drugs: when is statistically significant clinically significant? J Clin Invest 1997;99:2297-8.

77. Klein HO, Lang R, Weiss E, et al. The influence of verapamil on serum digoxin concentration. Circulation 1982;65:998-1003.

78. Kuhlmann J. Effects of quinidine, verapamil and nifedipine on the pharmacokinetics and pharmacodynamics of digoxin during steady state conditions. Arzneimittelforschung 1987;37:545-8.

79. Lee TH, Salomon DR, Rayment CM, Antman EM. Hypotension and sinus arrest with exercise-induced hyperkalemia and combined verapamil/propranolol therapy. Am J Med 1986;80:1203-4.

80. Abernethy DR. Pharmacological properties of combination therapies for hypertension. Am J Hypertens 1997;10:Suppl:13S-16S.

81. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. J Clin Pharmacol 1986;26:717-9.

82. Buhler FR. Age and cardiovascular response adaptation: determinants of an antihypertensive treatment concept primarily based on beta-blockers and calcium entry blockers. Hypertension 1983;5:Suppl III:III-94-III-100.

83. Abernethy DR, Schwartz JB, Todd EL, Luchi R, Snow E. Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients: altered electrocardiographic and hypotensive responses. Ann Intern Med 1986;105:329-36.

84. Schwartz JB, Abernethy DR. Responses to intravenous and oral diltiazem in elderly and younger patients with systemic hypertension. Am J Cardiol 1987;59:1111-7.

85. Abernethy DR, Gutkowska J, Winterbottom LM. Effects of amlodipine, a long-acting dihydropyridine calcium antagonist in aging hypertension: pharmacodynamics in relation to disposition. Clin Pharmacol Ther 1990; 48:76-86.

86. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. Clin Pharmacokinet 1992;22:416-33.

87. Schwartz JB. Calcium antagonists in the elderly: a risk-benefit analysis. Drugs Aging 1996;9:24-36.

88. The National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on hypertension in diabetes. Hypertension 1994;23:145-58.

89. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456-62. [Erratum, N Engl J Med 1993;330:152.]

90. Loutzenhiser R, Epstein M. Effects of calcium antagonists on renal hemodynamics. Am J Physiol 1985;249:F619-F629.

91. Dworkin LD, Benstein JA, Parker M, Tolbert E, Feiner HD. Calcium antagonists and converting enzyme inhibitors reduce renal injury by different mechanisms. Kidney Int 1993;43:808-14.

92. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int 1996;50:1641-50.

93. Bakris GL, Mangrum A, Copley JB, Vicknair N, Sadler R. Effect of calcium channel or beta-blockade on the progression of diabetic nephropathy in African Americans. Hypertension 1997;29:744-50.

94. Crepaldi G, Carta Q, Deferrari G, et al. Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. Diabetes Care 1998;21: 104-10.

95. Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKDPS 39. BMJ 1998;317:713-20.

96. Millard RW, Grupp G, Grupp IL, DiSalvo J, DePover A, Schwartz A. Chronotropic, inotropic, and vasodilator actions of diltiazem, nifedipine,

and verapamil: a comparative study of physiological responses and membrane receptor activity. Circ Res 1983;52:Suppl:I-29–I-39.

97. Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. II. Hemodynamic effects and clinical applications. Ann Intern Med 1980;93:886-904.

98. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990;82:1954-61.

99. Littler WA, Sheridan DJ. Placebo controlled trial of felodipine in pa-

tients with mild to moderate heart failure. Br Heart J 1995;73:428-33.

100. Dunselman PH, van der Mark TW, Kuntze CE, et al. Different results in cardiopulmonary exercise tests after long-term treatment with felodipine and enalapril in patients with congestive heart failure due to ischaemic heart disease. Eur Heart J 1990;11:200-6.

101. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Circulation 1997;96:856-63.

102. Hofer CA, Smith JK, Tenholder MF. Verapamil intoxication: a literature review of overdoses and discussion of therapeutic options. Am J Med 1993;95:431-8.